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10/599,349	08/22/2008	Frank Larsen	LARSEN	7245

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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/599,349	LARSEN, FRANK	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed November 18, 2010 is acknowledged. Claims 1, 10, 11, 14 and 18 (currently amended) and 2, 4-9, 12, 13 and 15-17 (previously presented) will be examined on the merits. Claims 3 and 19-23 have been canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 4-7 and 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 2004/001015) in view of Ronaghi et al. (U.S. Patent Pub.No. 2005/0084851).

With regard to claims 1 and 2, Wang teaches a method for determining a target nucleic acid sequence (methods are provided for reducing non-specific incorporation events in a sequencing by synthesis reaction, p. 1, lines 3-9 and p. 2, lines 19-20), the method comprising the steps of:

(a) contacting a preparation comprising the target nucleic acid sequence and a non-target nucleic acid sequence, the target nucleic acid sequence and the non-target nucleic acid sequence each having a first region of common sequence upstream of a first region of dissimilar sequence, with an oligonucleotide primer complementary to at least a portion of the first region of common sequence, under conditions to hybridise the

primer thereto (a single primer may be hybridized to a polymorphic nucleic acid, p. 4, lines 24-26 and p. 5, lines 26-28; see Example 3, where a single primer hybridizes to the two variations of SNP1 represented by the oligonucleotides 1T and 1C, p. 36, lines 18-22 and p. 37, lines 17-19); and

(b) subjecting the resulting preparation to a sequencing reaction, such that the sequencing reaction proceeds into the first region of dissimilar sequence of the target nucleic acid sequence, thereby determining at least the first region of dissimilar sequence of the target nucleic acid sequence (the sequencing primer is elongated by addition a single nucleotide, and after removing unincorporated nucleotides, the process is repeated until the desired sequence is obtained, p. 4, lines 27-32 and p. 5, lines 1-3); and wherein the method further comprises a step of blocking the sequencing reaction between the primer and the non-target nucleic acid sequence, such that the sequencing reaction does not proceed beyond the first region of dissimilar sequence of the non-target nucleic acid sequence (elongation of the sequencing primer may be terminated at a predetermined position by addition of blocking agent, preventing further elongation beyond the blocked site, p. 5, lines 4-5; see Example 3, where addition of ddA and/or ddG will terminate elongation of SNP1 and thus identify the polymorphisms, p. 38, top panel of table; thus, if a template or templates were used that possessed the same primer regions but one lacked the region complementary to the blocker, then sequencing or amplification of the template lacking the blocker site would proceed beyond the blocked site to allow distinguishing between two templates with the same

common primer region but varying in putative blocking regions, p. 21, line 22 to p. 22, line 2),

wherein the blocking step comprises contacting the preparation with a terminator nucleotide, under conditions to incorporate the terminator nucleotide into the extended or unextended primer hybridised to the non-target nucleic acid sequence but not into the extended or unextended primer hybridised to the target nucleic acid sequence (the blocking agent may be a non-extendable nucleotide, p. 5, lines 16-17; when ddG is added to the reaction, the 1T reaction is not blocked, while the 1C reaction is terminated, p. 38, lines 1-3).

With regard to claim 4, Wang teaches a method wherein the conditions are such that the terminator nucleotide is incorporated into substantially all of the extended or unextended primer hybridised to the non-target nucleic acid sequence (reaction conditions include about 1-1.5 pmole of each target nucleic acid and an excess of primers and each nucleotide, one at a time, wherein unincorporated nucleotides are removed by washing before the next round of synthesis, p. 4, lines 27-32 and p. 37, lines 7-16).

With regard to claim 5, Wang teaches a method wherein contacting the preparation with the terminator nucleotide is after step (a) and before step (b) of claim 1 (primers are added prior to initiating the elongation by addition of nucleotides and terminating nucleotides, p. 4, line 26 to p. 5, line 5).

With regard to claim 6, Wang teaches a method wherein the terminator nucleotide is complementary to a first nucleotide comprised in the first region of

dissimilar sequence of the non-target nucleic acid sequence, but the terminator nucleotide is not complementary to a second nucleotide at a corresponding position in the target nucleic acid sequence (the dideoxy terminator ddG may be added following hybridization of the primer to SNP1, and thus the terminator is complementary to the first position C of the non-target nucleic acid sequence but is not complementary to the first position T of the target nucleic acid sequence, p. 37, lines 17-19 and p. 38, lines 1-3).

With regard to claim 7, Wang teaches a method wherein the terminator nucleotide is a dideoxy nucleotide (the chain terminating nucleotides are dideoxynucleotides, p. 37, lines 29-30 and p. 38, lines 1-3).

With regard to claims 9 and 10, Wang teaches a method wherein the first region of dissimilar sequence comprises a single nucleotide (the region of the targets of SNP1 differ by a single nucleotide at position 36, p. 36, lines 18-22).

With regard to claims 11 and 12, Wang teaches a method wherein the sequencing reaction comprises a method of sequencing based on detection of released pyrophosphate, wherein the sequencing reaction comprises pyrosequencing (sequencing is performed by detecting incorporation events into the template that simultaneously releases pyrophosphate in an amount that is proportional to the amount of the nucleotide incorporated, and uses luciferase and luciferin or luciferase and ATP sulphurylase in combination to identify release of pyrophosphate by measuring the amount of light generated upon release of each pyrophosphate, as measured by a luminometer, p. 17, line 31 to p. 18, line 22 and p. 37, lines 29-33).

With regard to claim 13, Wang teaches a method wherein said preparation comprises DNA derived from two or more individuals subjects (samples may be derived from a wide variety of sources such as body fluids, and since the samples may be unpurified, may contain multiple types of nucleic acids, including different pathogenic organisms, p. 27, lines 3-14 and 20-22; forensic samples may be tested that may contain nucleic acid from more than one subject, p. 28, lines 6-14; the methods may also be used to simultaneously sequence alleles from different individuals, such as prospective tissue donors/recipients or in paternity testing, p. 32, lines 13-15).

With regard to claims 14 and 15, Wang teaches a method for determining a plurality of target nucleic acid sequences (methods are provided for reducing non-specific incorporation events in a sequencing by synthesis reaction, p. 1, lines 3-9 and p. 2, lines 19-20; the methods can be extended to multiplexing formats in which the identify of several nucleotides, or the identity of a nucleotide at multiple variant sites is determined in a single reaction, p. 22, lines 16-18) which method comprises the steps of:

(a) contacting a preparation wherein the plurality of target nucleic acid sequences is comprised in a preparation comprising a plurality of target nucleic acid sequences and a plurality of corresponding non-target nucleic acid sequences, wherein each target nucleic acid sequence in the preparation corresponds to one or more corresponding non-target nucleic acid sequences in the preparation, each target nucleic acid sequence and each corresponding non-target nucleic acid sequence has a first region of common sequence upstream of a first region of dissimilar sequence, the first region of common

sequence of each target nucleic acid sequence is the same as the first region of common sequence of its corresponding non-target nucleic acid sequences, the first region of dissimilar sequence of each target nucleic acid sequence is different to the first region of dissimilar sequence of its corresponding non-target nucleic acid sequences (multiple variant sites can be tested by the methods wherein the multiple sites may be within the same gene or different genes and different primers can be used for each of the sites, p. 22, lines 16-26), with a plurality of oligonucleotide primers, wherein each primer is complementary to at least a portion of the first region of common sequence of a target nucleic acid sequence and its corresponding non-target nucleic acid sequence, under conditions to hybridise the primer thereto (multiple primers may be hybridized to multiple polymorphic nucleic acids, p. 5, lines 23-27; see Example 3, where a single primer hybridizes immediately upstream to the two variations of SNP1 represented by the oligonucleotides 1T and 1C, while other primers hybridize to each of SNP2-4, p. 36, line 18 to p. 37, line 28); and

(b) subjecting the resulting preparation to a sequencing reaction, such that the sequencing reaction proceeds into the first region of dissimilar sequence of the target nucleic acid sequences, thereby determining at least the first region of dissimilar sequence of each target nucleic acid sequence (each sequencing primer is elongated by addition a single nucleotide, and after removing unincorporated nucleotides, the process is repeated until the desired sequence is obtained for each target sequence, p. 4, lines 27-32 and p. 5, lines 1-3); and wherein the method further comprises a step of blocking the sequencing reaction between each primer and each corresponding non-

target nucleic acid sequence, such that the sequencing reaction does not proceed into the second region of dissimilar sequence of each corresponding non-target nucleic acid sequence (elongation of the sequencing primers may be terminated at a predetermined position by addition of blocking agent, preventing further elongation beyond the blocked site, p. 5, lines 4-5; see Example 3, where addition of different dideoxynucleotides will terminate elongation of the primers used for the different SNP targets and thus identify the polymorphisms, p. 38, top panel of table; thus, if a template or templates were used that possessed the same primer regions but one lacked the region complementary to the blocker, then sequencing or amplification of the template lacking the blocker site would proceed beyond the blocked site to allow distinguishing between two templates with the same common primer region but varying in putative blocking regions, p. 21, line 22 to p. 22, line 2),

wherein the blocking step comprises contacting the preparation with a terminator nucleotide, under conditions to incorporate the terminator nucleotide into the extended or unextended primer hybridised to the non-target nucleic acid sequence but not into the extended or unextended primer hybridised to the target nucleic acid sequence (the blocking agent may be a non-extendable nucleotide, p. 5, lines 16-17; when ddG is added to the reaction, the 1T reactions is not blocked, while the 1C reaction is terminated, p. 38, lines 1-3).

With regard to claim 16, Wang teaches a method for determining the haplotype of a subject from a sample comprising DNA from the subject, wherein the preparation comprises the sample, the target nucleic acid sequence includes a locus on a first

chromosome of a pair of chromosomes, the non-target nucleic acid sequence comprises the corresponding locus on the second chromosome of the pair, the locus comprising two or more single nucleotide polymorphisms for which the subject is heterozygous, wherein the sequencing reaction is conducted to determine the sequence of the locus on the first chromosome of the pair thereby determining the haplotype of the subject (the methods may be used for sequencing samples to determine alleles of interest present in an individual's genomic DNA on each pair of chromosomes to provide the tissue type of the individual and whether the individual is homozygous or heterozygous for the alleles of interest, p. 32, lines 9-13).

With regard to claim 17, Wang teaches a method wherein the locus comprises a human Class I or Class II HLA gene (the methods may be used for sequencing samples to determine HLA alleles, including Class I and Class II alleles, p. 32, lines 15-25).

With regard to claim 18, Wang teaches a method of pyrosequencing a sample of DNA from a subject for determining the haplotype of the subject comprising the steps of: pyrosequencing a target locus on a first chromosome of a pair, the target locus comprising two or more single nucleotide polymorphisms, and blocking from sequencing the corresponding locus on the second chromosome of the pair by incorporation of a terminatore nucleotide into an oligonucleotide primer hybridized to the second chromosome (a pyrosequencing reaction is used in combination with dideoxynucleotides to determine sequences of templates varying by a single nucleotide, such as those represented by alleles such as HLA that may differ in sequence by one position, p. 32, lines 15-21 and p. 37, lines 29-33, see Table on p. 38, showing

differential incorporation of dideoxynucleotides into different sites of each SNP template that are complementary to each terminator).

Wang does not teach a method wherein the target and non-target sequences have a second region of dissimilar sequence downstream from a corresponding first region of dissimilar sequence, wherein the second region of dissimilar sequence comprises a single nucleotide, or wherein the target and non-target sequences each have a second region of common sequence which lies between the first and second regions of dissimilar sequence, or wherein the target nucleic acid sequence and the non-target nucleic acid sequence comprise one or more further regions of dissimilar sequence downstream of the second region of dissimilar sequence.

Ronaghi teaches methods of genotyping one more nucleic acid molecules that may contain two or more sites at which its sequence may be variable relative to a reference nucleic acid, comprising simultaneously or sequentially performing two or more primer extension reactions at different predetermined sites to generate a pattern of nucleotide incorporation, which is compared with one or more reference patterns obtained from control samples (see Abstract, paragraph 17, lines 1-9 and paragraph 19, lines 1-7). Ronaghi further teaches that a single variable site may be of any length, preferably 1 to 10 nucleotides, or more typically, 1 to 3 nucleotides, paragraph 32, lines 22, and that a single primer may be used to type variable regions that are located preferably within 20 nucleotides of each other, paragraph 23, lines 12-20). Ronaghi further teaches that to determine the sequence, nucleotides are added in a pre-determined order and may include dideoxynucleotides as chain terminators (paragraph

35, lines 1-15, paragraph 52, lines 1-27 and paragraph 80, lines 1-13) and that sequencing products may be detected by a pyrosequencing technique, paragraph 64, lines 1-3, paragraph 66, lines 1-9, paragraph 67, lines 1-19 and paragraph 117, lines 1-15).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Wang and Ronaghi since both references teach methods for genotyping nucleic acid samples by obtaining and comparing sequence information from test and reference nucleic acid samples. Furthermore, both references teach sequencing methods based on use of dideoxynucleotides as chain terminators and detecting sequencing products by pyrosequencing techniques. While Wang teaches methods of typing nucleic acid sequences that contain single nucleotide variant sites relative to a reference nucleic acid, Ronaghi teaches that variable sites may comprise dissimilar sequences of 1-10 nucleotides relative to reference sequences or that a single primer may be used to type variable sites separated by up to 20 nucleotides (Ronaghi, paragraph 32, lines 22 and paragraph 23, lines 12-20). Thus, an ordinary practitioner would have been motivated to use the methods of Ronaghi for typing nucleic sequences containing variable sites comprising more than one nucleotide or multiple sites within 20 nucleotides of a single primer binding site in the genotyping methods of Wang since the methods are highly compatible, each based on incorporation of dideoxynucleotides as chain terminators and detecting sequencing products by pyrosequencing techniques. Like Ronaghi, Wang teaches that multiple variable sites may be located on the same target nucleic

acid, within the same gene or at sites in different genes and that such formats allow for rapid sequence determinations in many loci and/or individuals simultaneously (Wang, p. 22, lines 16-21). It would have been obvious to an ordinary practitioner to include more complex types of variable sites in the methods of Wang, such as those taught by Ronaghi, which include sites that extend multiple bases or where multiple variable sites are located near a common primer site to allow a single sequencing assay with a single primer to obtain information for both sites. Furthermore, Ronaghi teaches that their method, also like that of Wang, is particularly suited to automation, such as could be performed in a microtiter place format, and is ideal for identifying microbial species and subtypes as well as typing of polymorphisms such as tissue typing or in clinical applications (paragraph 14, lines 1-7). Ronaghi further teaches that their invention is advantageous in that it determines the exact sequence of the variable sites without cumbersome procedures such as electrophoresis, and can analyze large numbers of samples in a short time (Ronaghi, paragraph 99, lines 1-6).

4. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 2004/001015) in view of Ronaghi et al. (U.S. Patent Pub.No. 2005/0084851) as applied to claims 1, 2, 4-7 and 9-18 above, and further in view of Stanton, V.P. (U.S. Patent Pub. No. 2003/0082537).

Wang and Ronaghi together teach the limitations of claims 1, 2, 4-7 and 9-18, as discussed above. However, neither Wang nor Ronaghi teach a method wherein the

terminator nucleotide is capable of covalently cross-linking the primer to the non-target nucleic acid.

Stanton teaches a method for determining genotypes and haplotypes of genes, including single nucleotide polymorphisms, by standard methods of chain-terminating DNA sequencing reactions, wherein one of the two alleles of interest is enriched by methods such as cross-linking the desired allele with a complementary oligonucleotide by cross-linking agents to protect the allele from degradation by exonucleases (paragraph 142, lines 1-18, paragraph 143, lines 1-10, paragraph 229, lines 1-11 and Figure 41).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Wang and Ronaghi for genotyping using dideoxynucleotide chain terminators and pyrosequencing with those of Stanton for genotyping since the methods for enrichment of alleles taught by Stanton are highly compatible with the methods of Wang and Ronaghi. Thus, an ordinary practitioner would have been motivated to use the methods of Stanton for enrichment of desired alleles using cross-linking agents since the enriched sample is available for any genotyping methodology, whether it be DNA or cDNA, to determine the genotype and haplotype of the remaining allele that is resistant to exonuclease degradation (Stanton, paragraph 230, lines 11-19). Furthermore, Ronaghi teaches that their method, also like that of Wang, is particularly suited to automation, such as could be performed in a microtiter place format, and is ideal for identifying microbial species and subtypes as well as typing of polymorphisms such as tissue typing or in clinical applications

(paragraph 14, lines 1-7). Ronaghi further teaches that their invention is advantageous in that it determines the exact sequence of the variable sites without cumbersome procedures such as electrophoresis, and can analyze large numbers of samples in a short time (Ronaghi, paragraph 99, lines 1-6).

Response to Arguments

5. Applicant's arguments filed November 18, 2010 have been fully considered but they are not persuasive.

Applicant argues that the rejection of claims 1-7 and 9-19 under 35 U.S.C. § 103(a) as being obvious over Wang et al. (WO 2004/001015) in view of Ronaghi et al. (U.S. Patent Pub.No. 2005/0084851) should be withdrawn since the combination of the references no longer teaches all the limitations of the claims as amended. In particular, Applicant argues that Wang teaches methods of using sequencing primers that specifically bind to two target sequences that differ from each other in only one nucleotide position near the 5'-end of the primer, and thus detect one particular nucleotide difference or SNP in the two target nucleic acids, as exemplified in Example 3 of Wang. Thus, Applicant argues that Wang fails to disclose methods wherein two consecutive regions of dissimilar sequence are analyzed simultaneously, such as two consecutive SNPs. Applicant further argues that, contrary to the teachings of Wang, the instant invention does not require inclusion of a short insertion into the non-target nucleic acid for blocking a sequencing reaction. In addition, Applicant argues that Wang does not disclose details of the blocking of the sequencing reaction, including the

chemical nature of the blocker. Finally, Applicant argues that the disclosure of Ronaghi, while being a parallel fingerprinting method to that of Wang, fails to provide the missing elements of Wang, and furthermore that the Examiner has failed to specifically reference the missing elements in Ronaghi.

As discussed above, the Examiner has stated that Wang does not teach methods wherein target and non-target sequences have more than one dissimilar sequence. However, contrary to Applicant's assertions, the claims do not require that the two or more dissimilar sequences be consecutive, such as consecutive SNPs, only that there are two regions of dissimilar sequence. The Examiner asserts that Wang teaches methods for blocking one sequencing reaction wherein a site is complementary to the blocker, while a primer is extended beyond the site in a sequence sharing the same priming site but lacking the complementary blocking site. Though Wang teaches an additional embodiment wherein a short insertion is included in the non-target sequence, the Examiner is not citing this teaching in the rejection. The Examiner further asserts that Wang teaches method of blocking sequencing reactions using dideoxynucleotide triphosphates (see p. 19, lines 5-28, p. 38, lines 1-12 and Table on p. 38). With regard to the disclosure of Ronaghi, the reference teaches genotyping methods similar to those of Wang wherein two or more primer extension reactions are performed, with the additional feature that detection of two or more variable sites are possible using a single primer that is within 20-50 nucleotides of the variable sites (see paragraph 23). Thus, two or more closely spaced SNPs may be detected using a single primer, while a second primer would be required if the variable sites are more distant

from each other. One of skill in the art would be motivated to combine the methods of Wang and Ronaghi since both methods are highly compatible and use the same types of blocking agents, dideoxynucleotide triphosphates, as chain terminators and detect sequencing products by the same pyrosequencing techniques. Therefore, for all the reasons stated above, the 103 rejection of claims 1, 2, 4-7 and 9-18 over Wang in view of Ronaghi is maintained.

Applicant then argues that the rejection of claim 8 under 35 U.S.C. § 103(a) as being obvious over Wang in view of Ronaghi and further in view of Stanton, V.P. (U.S. Patent Pub. No. 2003/0082537) should be withdrawn since the combination of the references no longer teaches all the limitations of the claims as amended. In particular, Applicant argues that while claim 8 cites a covalent cross-linking of the primer to the non-target nucleic acid, Stanton discloses that the cross-linking is achieved by chemical means to the target DNA, and that the respective cross-linking reactions represent two very different reactions and very different steps. Applicant further contends that the Examiner relied upon hindsight to arrive at the determination of obviousness, in that there is no teaching or suggestion in the references to support the proposed combination. The Examiner asserts that Stanton teaches a method of cross-linking a thiophosphorthioate-modified oligonucleotide to a polymorphic site that, like the cross-linking step as claimed, is of a covalent nature to one of the two nucleic acids in question (see paragraphs 142 and 230). Furthermore, while the claimed method cites cross-linking of a primer to the non-target nucleic acid, Stanton teaches a method of cross-linking to the target nucleic acid that is functionally the same, since the two

methods both allow the target and non-target nucleic acids to be distinguished. Since both references teach methods of genotyping polymorphic sites, it would be obvious to one of skill in the art to use a cross-linking method such as that taught by Stanton to prevent primer degradation for identification of the sequence of the polymorphic site. Therefore, the 103 rejection of claim 8 over Wang in view of Ronaghi and further in view of Stanton is maintained.

Summary

6. Claims 1, 2 and 4-18 are rejected. No claims are allowable.

Conclusion

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637